REMARKS/ARGUMENTS

Claims 37-39 are pending and under examination.

The Examiner has maintained the obviousness rejections. Applicants respectfully traverse.

Declarations filed with response filed January 8, 2007

First, the response filed January 8, 2007 included two Declarations under 37. C.F.R. § 1.132. The first of these is the Declaration under 37 C.F.R. § 1.132 that was made by Joe W. Gray, which is discussed in the current office action. The second is a Declaration of Inventorship under 37 C.F.R. § 1.132 by Joe Gray and Laleh Shayesteh.

The second Declaration filed January 8, 2007 was apparently overlooked by the Examiner. Drs. Gray and Shayesteh (formerly Daneshvar) are co-authors of the cited reference Daneshvar *et al., Am. J. Human Genetics* 59: No. 4 SUPPL, page A65, November 1996 ("Daneshvar"). This Declaration attests that to the extent that the claimed subject matter is taught or suggested by Daneshvar, it is the work of the inventors named on the present application. In view of the submission of this Declaration, Daneshvar is removed as a prior art reference. A copy of this previously-filed Declaration and a postcard showing receipt at the PTO is attached for the Examiner's convenience.

Rejection of claims 37 and 38-Bonjouklian, Arnold, Volinia, and Xiao or Skorski

The Examiner has maintained the rejection of claims 37 and 38 as allegedly unpatentable over Bonjouklian in view of Arnold and Volinia and further in view of Xiao or Skorski. Applicants traverse this rejection for reasons of record. In brief, Applicants have discovered that amplification of the particular subregion at 3q26.3, including *PIK3CA*, is of diagnostic significance for cancer and further, that amplification of *PIK3CA* is in fact associated with increased PIK3CA expression and ovarian cancer cell proliferation. Applicants have thus determined that cancer cells that contain an amplification of PIK3CA are therapeutic targets for PIK3CA kinase inhibitors. Prior to this discovery, it was not evident that simply because 3q26-

3qter had been observed to be amplified in ovarian cancer, PIK3CA would be an important diagnostic and therapeutic target. The rejection appears to rest on the position that an amplification of a large chromosomal region such as 3q26-qter would lead to overexpression of the genes contained within that region and accordingly, that cells harboring an amplification at 3q26 would also exhibit increased PIK3CA expression and therefore, according to the Examiner, qualify as "PIK3CA-dependent" neoplasms. However, as Applicants have previously noted, this position is inconsistent with the facts.

The Examiner also contends that the Declaration under 37 C.F.R. § 1.132 by Dr. Joe Gray filed January 8, 2007 ("Gray I") is insufficient to establish that amplification of 3q26-3qter would not reasonably be expected to lead to overexpression of the PIKE3CA gene. The Examiner alleges that Dr. Gray's statements in the Gray I Declaration are merely conclusory and that other evidence suggests the opposite conclusion. Although Applicants disagree with this characterization of the Gray I Declaration, provided herewith is a second Rule 1.132 Declaration by Dr. Joe Gray (Gray II) that provides more explicit details with regard to this issue.

Gray II Declaration

In the Gray II Declaration, Dr. Gray provides additional evidence that amplification does not necessarily correlate with overexpression . As an example, Dr. Gray provides a publication by Chin *et al.* (2006) *Cancer Cell.* 10:529-4 ("Chin", Exhibit A of the Declaration). Chin evaluated breast cancer and the correlation of amplification of four different chromosomal regions with overexpression of gene product. As Dr. Gray explains, Chin demonstrates that, in reality, although chromosomal amplification are common in cancer, increased expression of genes within these amplicons happens only in a minority of cases.

Dr. Gray further describes work performed in his laboratory in which 68 genes from the 3q26 regionsof amplification were analyzed. Of these, only 30 had expression levels that were associated with copy number.

In section 10 of the Gray II Declaration, Dr. Gray further explains that regardless of the number of genes in the amplified region, prior to Applicants' invention, one of skill could not conclude that amplification would lead to overexpression of *PIK3CA* and activation of

phosphoinositide 3-kinasee because transcriptional upregulation of a gene frequently does not lead to increased protein expression, and expression of one subunit of a signaling complex would not necessarily lead to increased activity of the complex. The inventors demonstrated that in fact, amplification and overexpression of *PIK3CA* is associated with increased PI3-kinase activity and that treatment with the PI3-kianse inhibitor decreases proliferation and increases apoptosis.

Finally, in section 11, Dr. Gray points out that despite the fact that it is known that 3q26 is amplified, the identification of a potential role of other genes in this region in ovarian cancer warranted publication in high-rank journals. This provides additional evidence that those in the art do not consider the simple presence of a gene in an amplified region to predict utility as a therapeutic target.

Grimaldi Declaration in light of Gray II Declaration

The rejection cites a declaration by Dr. Grimaldi that the Examiner characterizes as opposing the conclusions of the Gray I Declaration. Specifically, the Examiner cites paragraph 4 of the Grimaldi declaration where Dr. Grimaldi states that "[C]hromosomal aberrations, such as gene amplification, and chromosome translocations are important markers of specific types of cancer and lead to the aberrant expression of specific genes and their encoded polypeptides, including over-expression and under-expression." The Examiner interprets this passage as making an express connection between gene amplification and over-expression. This interpretation of Grimaldi's statement in the office action is, however, faulty. Applicants do not dispute that gene amplification can lead to overexpression. The key point is that amplification frequently does not lead to overeexpression. Grimaldi states that amplification leads to the aberrant expression of specific genes and their encoded polypeptides; not that amplification is so generalized that it necessarily leads to overexpression of genes. In contrast, Dr. Gray has provided direct evidence that amplification and overexpression indeed do not correlate.

Size of amplification

Thee Examiner characterizes the region of amplification that was described in the prior art as "small". However, Arnold in fact describes a very large region of amplification, 3q26-qter. As Dr. Gray explained in the Gray I Declaration, this region harbors many, many genes and the techniques employed by Arnold are insufficient to be able to ascertain that 3q26.3 is a focal point of amplification.

The Gray II Declaration provides additional details regarding the large number of genes present in the region described by Arnold. Dr. Gray provides a printout of information from the Ensembl genome browser that provides more detailed information as to the number of genes that have been identified in this chromosomal region. Exhibit F provides a graphic of the region of chromosome 3 from q26.1 through q29. Exhibit F also shows the genes contained within this region (Chromosome 3 162152104-199501827), of which there are hundreds. Exhibit C focuses on the 3q26 region, *i.e.*, 3q26.1 through 3q26.33. A listing of the genes identified in that region (Chromosome 3 162152104-184145606) shows that there about 85 genes in this region alone. Accordingly, the region identified by Arnold as amplified in ovarian cancer, 3q26-3qter, in fact contains a large number of genes, as does the subregion of 3q26, as noted in the Gray I Declaration.

The Examiner contends that the single parameter of over-expression need be determined from "only" about 30-50 different genes in total, referring to the data allegedly shown in the Gray I declaration. However, the Gray I Declaration only showed a representative number of genes in the area of amplification identified in the prior art. As explained above, there are more than 50 genes in the region. Even assuming that 30-50 genes would be considered "reasonable" in terms of evaluating overexpression and correlation with cancer and gene amplification (which Applicants do not concede), Arnold teaches that the amplification area is 3q26-3qter and further, teaches that it is this whole region that is of interest. For example, Arnold points to a gene encoding a zinc finger, BCL6, that is located in the amplified area that may be of interest as a potential oncogene. BCL6 is located at 3q27.3 (see, e.g., the printout from the Ensemble genome browser). Thus, the prior art teaches that a very large region, 3q26-

3qter, is amplified and does not narrow the region of interest. The Gray II Declaration establishes that there are hundreds of gene 3q26-3qter.

Thus, Gray II not only provides evidence that amplification does not correlate with overexpression, but also shows that there are many, many genes in the amplified region identified by Arnold. In light of the facts, the genes present in 3q26-3qter, including the genes present at 3q26 in particular, could not be characterized as "predictable solutions" to the problem of identifying cancer cells that are targets for PIK3CA kinase inhibitor therapy.

Legal standards

Pfizer Inc v. Apotex Inc, 82 USPQ2d 1321 (Fed. Cir. 2007) is cited in the office action as allegedly supporting the Examiner's position that the claims are obvious. However, the facts here are not analogous to those in *Apotex*. In *Apotex*, there were about 50 salts to be tested. These salts were known to be useful in making pharmaceutical formulations. The Federal Circuit concluded that Pfizer would have had a reasonable expectation of success for various reasons including the following: Pfizer conceded in prior litigation that the type of salt had no effect on the therapeutic effect of the active ingredient, amiodipine, and was practically interchangeable; and numerous other publications clearly directed the skilled artisan to a pharmaceutically-acceptable acid-addition salt made from benzenesulphonate, including the besylate acid addition-salt for another dihydropyridine pharmaceutical compound.

Such a reasonable expectation of success is not present here. There are many, many genes present in 3q26-qter, even in the subregion 3q26. Unlike *Apotex*, where all of the 50 salts were acknowledged to be useful in making a pharmaceutical formulation, there is no evidence that any of these particular genes would be expected to be overexpressed and play a role in ovarian cancer. As Dr. Gray noted in the Gray I Declaration, it was simply not possible to determine the focal point of amplification in the studies described by Arnold. Volinia's observation that PIK3CA is localized to 3q26.3 provides no indication that it would be expected to play a role in ovarian cancer in which 3q26-3qter is amplified. The studies of Xiao and Skorski that look at PIK3CA activity in gastric cancer cell lines and leukemia cells do not provide any insights into ovarian cancer. The evidence provided by Applicants demonstrate that

it is unpredictable whether any particular gene, even if it is amplified, would play a role in cancer, given the complexity of the disease. Thus, in the present case, there is no finite number of identified predictable solutions. Accordingly, even under the standard of obviousness articulated by the Supreme Court in *KSR International Co. V. Telefex Inc.* 82 USPQ2d 1385 (S. Ct. 2007), the claims are patentable. Applicants therefore respectfully request withdrawal of the rejection.

Rejection of claims 37 and 38-Bonjouklian, Daneshvar and Xiao or Skorski

Next, the Examiner cites Daneshvar as specifically connecting ovarian cancer and PIK3CA. The Examiner cites the Ashkenazi Declaration as evidence that one of skill would have found that a gene that is both amplified and overexpressed is "a promising target for cancer therapy". As noted above, the 1.132 Declaration by Gray and Shayesteh (formerly Daneshvar) removes the reference as prior art.

With regard to Ashkenazi, Ashkenazi states that '[i]f gene amplification results in oeverexpression of the mRNA and the corresponding gene product..." For the reasons explained above it is unlikely that any given particular gene that is amplified is also overexpressed.

In view of the foregoing, Applicants request withdrawal of this rejection.

Rejection of claim 39-Bonjouklian, Arnold, Volinia, and Xiao or Skorski in view of Powis or alternatively in view of Lavin or in view of June

The rejection of claim 39 as allegedly unpatentable over Bonjouklian, Arnold, Volinia, and Xiao or Skorski as applied to claims 37 and 38 above, and further in view of Powis, or alternatively, in view of Lavin or in view of June is also maintained. The Examiner contends that one of skill would have been motivated to use LY294002 in the methods of the invention, because it was known to be an effective inhibitor of PI3 kinase, as evidenced by any of the three secondary references. Applicants respectfully traverse this rejection. The cited art (Bonjouklian, Arnold, Volinia, and Xiao or Skorski) applied to claims 37 and 38 fails to establish a proper case of obviousness for the reasons explained above. The secondary references merely teach that LY294002 is a PI3 kinase inhibitor. Such disclosure does not cure the defects in the Examiner's

arguments based on the primary references. Accordingly, claim 39 is patentable over the cited art. Applicants therefore respectfully request withdrawal of the rejection.

Rejection of claim 39-Bonjouklian, Daneshvar, and Xiao or Skorski in view of Powis or alternatively in view of Lavin or in view of June

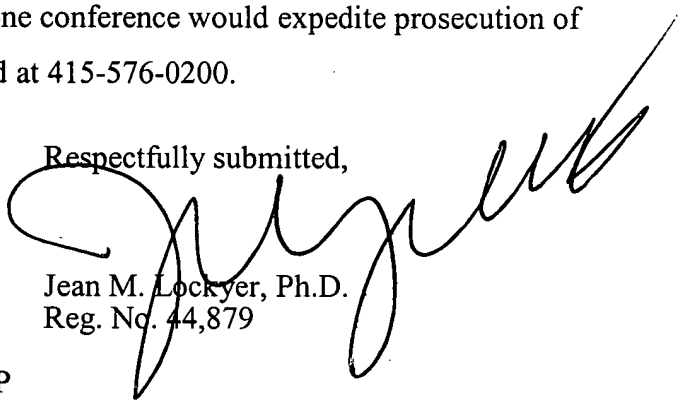
Claim 39 was also rejected as allegedly unpatentable over Bonjouklian, Daneshvar, and Xiao or Skorski as applied to the rejections of claims 37 and 38 above, and further in view of Powis, or alternatively, in view of Lavin or in view of June. Daneshvar is not available as a prior art reference in view of the submission of the Declaration of Inventorship under 37 C.F.R. § 1.132. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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